



Dipartimento
di Salute Mentale

Sistema Socio Sanitario



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The implementation of evidence based psychosocial/rehabilitative interventions in patients with early schizophrenia treated continuously with antipsychotics: a prospective observational study in Italy

Background:

The Italian document Stato Regioni (an agreement between Italian Government and local regions) (1) analyses priority objectives indicated by the PANSM (Piano Nazionale di Azioni per la Salute mentale - National Plan of Actions for Mental Health) to identify pathways of care for severe mental illnesses (schizophrenia, affective disorders and severe personality disorders) which should be offered by Italian Departments of Mental Health in order to reduce the variability of treatments and to increase the quality of the service offered and the efficiency of resource use. As for schizophrenia, it is underlined the importance that the patient is offered an integrated treatment which involves a multiprofessional team and the application of several clinical and psychosocial and rehabilitative interventions based on the scientific evidence and guidelines recommendations. The proposal of activities should be linked to the patient degree of functional impairment or disability in order to improve patient's functioning and level of personal and social autonomy. This consideration is consistent with the evidence that antipsychotic therapy alone, even if effective on some clinical parameters, should be integrated with psychosocial and rehabilitative interventions to achieve better outcomes in terms of personal and social functioning and quality of life (2) and that "evidence-based" psychosocial treatments (such as cognitive behaviour therapy for psychosis, cognitive remediation, family psychoeducation, social skills training and supported employment) are considered more effective than nonspecific and unstructured interventions (3), which, however, are more often implemented in the psychiatric services. In a Survey recently performed in Lombardia Region the frequency with which community health centers offer their patients any evidence based rehabilitative intervention has been found to be less than 10% (4), while a percentage of about 18% of subjects undergoing EB treatments (including supported employment) emerged in a wider national Survey promoted by the Italian Society of Psychosocial Rehabilitation (SIRP National Congress, Salerno, 2014; SIP National Congress, Taormina, 2015). Unfortunately, transversal or retrospective study designs do not allow to assess accurately the frequency of implementation of specific interventions, which are differently defined and applied in different contexts, and to characterize the clinical-functional features of patients assigned to them. The Stato- Regioni document underlines also the importance of proposing an integrated multidisciplinary approach as soon as possible after the diagnosis of schizophrenia and the crucial importance of the continuity of treatment with antipsychotics from the onset of psychosis onward. Unfortunately, no data are available on the implementation of EB treatments in patients treated continuously with antipsychotics in the early phases of the disease.

In front of the importance of offering a wide range of activities to the patient, a high variability of treatments is offered in the different Italian psychiatric departments, with no data available for most Italian regions and, even in the case of the more advanced regions, with a low delivery rate of evidence-based psychosocial activities as compared with other non-evidence-based psychosocial activities. The pharmacological continuity is a challenge as well. Literature data confirm the importance of poor adherence which may cause not only the occurrence of relapses and re-hospitalizations but also other

negative outcomes for the patient, such as the inability to access and maintain rehabilitative interventions and reintegration (5). Treatment with antipsychotics of patients suffering from schizophrenia should provide a good balance between efficacy, safety, tolerability and acceptability for the patient to determine its continuity (6) and the use of long-acting injection (LAI) antipsychotics is an effective response to these problems, ensuring better outcomes than oral treatment (7,8). In addition, drug treatment applied promptly and continuously is particularly important in order to prevent relapses in the early stages of schizophrenia thus limiting the functional deterioration which generally occurs within the first 5-10 years after the first episode and the clinical and psychosocial deterioration which occurs mostly within the first 5 years from the onset of the illness (9). Moreover, there is evidence in the literature that treatment of first episode patients with a LAI atypical antipsychotic increases treatment acceptability, adherence and the rate of sustained remission (10).

Given all these premises we are interested in observing how often Evidence Based (EB) psychosocial and rehabilitative interventions are actually offered to patients in the real world clinical practice of psychiatric Italian services able to deliver this kind of treatments, focusing on a cohort of patients with recent onset schizophrenia, for whom delivery of integrated treatments is especially recommended (1), treated continuously with LAI antipsychotics.

Study objectives:

The primary objective of this study is to explore the level of implementation of EB psychosocial/rehabilitative treatments during a prospective 12-month period in patients with recent onset schizophrenia (≤ 5 years) being treated with a LAI Antipsychotic in Psychiatric Departments with expertise in the application of such interventions and to describe the reasons of implementing the particular EB psychosocial intervention and the clinical-functional characteristics of patients assigned to them. The prospective design is strictly required both for allowing consistent definition and application of such interventions and for describing reliably the characteristics of patients assigned to them. Secondary objectives are to describe the reasons for the choice of the specific assigned psychosocial intervention (if any) and the clinical and functional treatment outcomes of patients assigned or not-assigned to EB psychosocial therapies.

Study design:

Prospective, observational, naturalistic study conducted according to Italian law (11-14).

The assignment of a patient to any particular treatment is not decided in advance by the study protocol, but falls within current clinical practice.

No additional diagnostic or monitoring tools apply to individuals, with the exceptions listed and allowed by the Italian legislation (11). The administration of questionnaires and scales is accepted by Italian law

regarding non-interventional studies (11).

All the parameters will be evaluated when available and collected for patient care.

A scientific committee approves the scientific rationale of the protocol and approves the final report.

The study will be conducted according to the protocol, the current version of the Declaration of Helsinki, the guidelines of Pharmacoepidemiology (12), and the Italian applicable regulations (11,13). According to the latter, patients will sign a written informed consent to participate. For each center involved, the investigator will provide all information to the subjects involved in the study in a form that the person is able to understand, and will obtain written consent before the collection of personally identifiable information. The data of consenting patients will be recorded in an electronic database.

Diagnosis and main criteria for inclusion / exclusion

Inclusion criteria:

- Patients with schizophrenia (F20 according to ICD-10 version 2013)
- Onset of schizophrenia, defined as the first onset of symptoms that required specific antipsychotic treatment or hospitalization, as derived from anamnesis or available clinical documentation, not more than 5 years before study entry
- Age between 18 and 50 years
- Patients under treatment with a LAI on the basis of physician's decision (LAI started no longer than 6 months before study entry) and clinically stable (no relapse requiring hospitalization or change of treatment due to clinical worsening) during the last 1 month.

Endpoints:

Primary outcome of interest ("endpoint") is percentage of patients within the total study population who have been assigned to any EB psychosocial/rehabilitative treatment (listed below) for at least 1 month consecutively during the 12-month observation period (given the heterogeneity of interventions, this is an arbitrary duration which may reliably indicate a significant exposure to a given intervention). The percentage of each type of psychosocial intervention delivered together with frequency of sessions and length of treatment, and the reasons (categorized) given by the clinicians to justify the selected psychosocial intervention as well as the clinical-functional characteristics of patients assigned to them will be described. Patient assignment to the different interventions and their delivery will be traced in the patients' clinical charts. A list of wordings to describe each intervention will be provided in order to identify reliably and univocally the activities delivered.

- Evidence Based interventions*:
 - a. Psychoeducation (15)
 - b. Social Skills Training (16)



- c. Cognitive remediation (17)
- d. Cognitive-behavioral Therapy for psychosis - CBTp (18)
- e. Work rehabilitation (19)

* Evidence-based interventions are defined as involving a multiprofessional team, having structured methodology, specified frequency and duration of sessions, and following manualized or otherwise standardized procedures

Secondary endpoints:

- Sociodemographic information
- Percentage of patients assigned during the 12-months period to at least one non EB intervention for at least 1 month consecutively (given the heterogeneity of interventions, this is an arbitrary duration which may reliably indicate a significant exposure to a given intervention) but not to any of the EB interventions.

- Non EB interventions**:

- a. music therapy
- b. expressive activities
- c. risocializing activities
- d. manual activities
- e. kitchen groups
- f. recreational activities
- g. motor activities

**Non Evidence-Based psychosocial interventions are defined as involving multiprofessional team, but with non-specified frequency and duration and without reference to manuals or standardized procedures

- Percentage of relapses (*)
- % of patients who discontinue drug treatment (for ineffectiveness, side effects or other reasons and patient/physician decision) and/or psychosocial interventions (for team or patient decision)
- Change of the CGI-SCH scale score (20) to assess the evolution of the severity of symptoms
- Change of the PSP (Personal and Social Performance) scale score (21) to assess the evolution of psychosocial functioning
- % of PSP responders (increase of 7 points of the total PSP score) (22,23)
- % of patients reaching a PSP score > 71
- Score change of the scales related to patient satisfaction with treatment: MSQ (Medication Satisfaction Questionnaire) (24) and SWN (Subjective Well Being on Neuroleptics) (25, 26)

- Score change of the SCoRS (Schizophrenia Cognition Rating Scale) (27) to assess the evolution of the severity of cognitive symptoms
- Safety assessments including monitoring of treatment-emergent adverse events

** In this naturalistic study, a relapse is defined as a psychiatric hospitalization or as an increase in the overall score of the CGI-SCH of at least two points when the minimum score for the patient during follow-up was 1 (normal), 2 (borderline) or 3 (mildly ill) or of 1 point when the minimum score was 4 (moderately ill), 5 (very ill), or 6 (seriously ill). The increase in the CGI score must take the patient to be at least moderately ill (CGI = 4).*

Additional endpoints:

- Health economic information collected through 3 specific questionnaires (28): detection of i) health resources consumption for the care of the disorder (direct costs, eg. drug cost, hospitalization, emergency visits, Day hospitals, GP visits...) and assessment of indirect costs through evaluation of : ii) patient's potential income loss, absenteeism and presenteeism to estimate work productivity, daily activity impairment due to the mental illness and of iii) caregiver's potential income loss, commitment of time for the patient's care, absenteeism and presenteeism to estimate work productivity, daily activity impairment because of the patient's mental illness.

Exploratory analyses

If data collected will allow, exploratory analyses will be done to compare clinical and functional outcomes among the potential group stratifications which are expected to be composed by:

- A. Patients treated with EB interventions
- B. Patients treated with non-EB interventions
- C. Patients who did not receive any EB or non-EB psychosocial/rehabilitative treatment

Evaluation criteria/study assessments:

Patients are seen in the context of usual clinical practice and data will be collected at baseline, and after 3, 6 and 12 months after recruitment (see flow chart). This visit program remains indicative, ie the intervals between visits are the usual intervals of each center and the closest to the expected time assessments will be considered for the study evaluations.

Health economic information will be collected at 6 and 12 months

Study assessments and recorded parameters are summarized in the flow chart at pag 6.

Statistics and sample size calculation

The primary variable of interest (primary endpoint) will be the proportion of the recruited patients who, in the course of the 12-month follow-up, will be assigned to at least 1 month of EB psychosocial treatment/rehabilitation.

Currently, reliable estimates of such proportion are not available and, in fact, this is expected to be surveyed through this study. In a Survey recently performed in Lombardia Region the frequency with which community health centers offer their patients any evidence based rehabilitative intervention has been found to be less than 10% (4), while in a wider national Survey about 18% of included subjects were receiving any kind of EB treatment, including supported employment (SIRP National Congress, Salerno, 2014; SIP National Congress, Taormina, 2015). No data at all are available on the implementation of EB psychosocial treatments in patients treated continuously with antipsychotics in the early phases of the disease. However, we believe that the proportion of patients on EB rehabilitative interventions in our study could be higher than those reported above. The participating centres are, in fact, able to apply effective EB psychosocial interventions. Moreover, the survey applies to patients in the early phases of schizophrenia (< 5 years of illness), i.e. a group of patients who should be assigned systematically to an integrated care according to the Stato- Regioni document (1), and more adherent to medication since treated continuously with LAI antipsychotics. As the reliability of our results depends on the proportion of patients on EB interventions, and as this proportion is still to be defined, we will use an hypothetical percentage of 50% in determining the sample size needed for a given level of accuracy. This assumption will prevent us from having an underpowered survey.

Eighteen is the number of centres identified and recruited to participate in the study. Overall, in 2014, 29527 patients were in charge at those centres. Of these, 4034 (14%) had a clinical presentation compatible with a diagnosis of schizophrenia (F20 according to ICD-10 version 2013) and 1462 (5%) were also being in therapy with LAI antipsychotics. On the basis of these data, it is estimated that eligible patients, namely those having a history of recent illness (<5 years), are approximately 1000, i.e. 5.5 per centre. According to an initial feasibility assessment, it is expected that each centre could include at least 15 patients. Providing a proportion of patients lost to follow-up almost irrelevant, given the ease of detection of the variable of interest, this will produce a sample of prevalence of 270 individuals with a two-tailed 95% Confidence Interval (CI) with a margin of error of around 5%.

The clinical and functional characteristics of patients assigned to EB psychosocial treatment / rehabilitation will be described.

Descriptive statistical analyses will be carried out by calculating the arithmetic mean and standard deviation (median and interquartile range for data with skewed distributions) for quantitative variables,



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and absolute frequency and percentage for qualitative variables. In addition, calculations will be made of the relevant confidence intervals (95%) for the clinically relevant variables.

If possible, exploratory comparisons of clinical and functional variables associated with the group stratifications generated naturalistically will be conducted.

The data will be entered into a database specifically created for the purposes of this study.

Statistical analyses will be made with SAS® version 9.2 and values of $P < 0.05$ will be considered statistically significant.

In synthesis

Study type: Prospective, observational, naturalistic study in the real world

Centers: 18 centers

Duration of study: 18 months recruitment, 12 months follow-up

Start date: December 2017

Recruitment period: 2017-18 - 19

Analyses provided: 2019-2020



FLOW CHART

Dati	Times	V1 (Baseline)	V2 3 months	V3 6 months	V4 12 months
Informed consent		√			
Inclusion/Exclusion criteria		√			
Sociodemographic information		√			
Anamnesis/Psychiatric history*		√			
Pharmacological treatment (LAI antipsychotics, other concomitant medications)		√	√	√	√
Psychosocial/rehabilitative treatment		√	√	√	√
Reason for the selected psychosocial intervention		√	√	√	√
Relapse			√	√	√
Discontinuation of AP			√	√	√
Discontinuation of rehabilitation			√	√	√
CGI-SCH		√	√	√	√
PSP		√	√	√	√
SCoRS		√	√	√	√
SWN		√	√	√	√
MSQ		√	√	√	√
AEs and SAEs		√	√	√	√
Health economic information		√		√	√



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